

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Vincent P. Stanton, Jr. Art Unit :
Serial No. : Examiner :
Filed : HEREWITH
Title : THYMIDYLATE SYNTHASE GENE SEQUENCE VARIANCES HAVING
UTILITY IN DETERMINING THE TREATMENT OF DISEASE

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the Title:

Replace the title with the following new title:

-- THYMIDYLATE SYNTHASE GENE SEQUENCE VARIANCES HAVING
UTILITY IN DETERMINING THE TREATMENT OF DISEASE--

In the specification:

Insert the enclosed Sequence Listing into the specification after the Oath and Declaration.

Replace the paragraph beginning at page 1, line 8, with the following new paragraph:

--This application is a divisional of U.S. Application Serial No. 09/658,659, filed

September 8, 2000, which is a CIP of Stanton, U.S. Application serial No. 09/596,033, filed June 15, 2000 entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton, U.S. Application 09/357,743, filed July 20, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton,

CERTIFICATE OF MAILING BY EXPRESS MAIL

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I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

September 24, 2001
Date of Deposit
Signature
Lisa G. Gray
Typed or Printed Name of Person Signing Certificate

U.S. Application Serial No. 09/357,024, filed July 19, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which claims the benefit of Stanton, U.S. Provisional Application 60/093,484, filed July 20, 1998, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which are all hereby incorporated by reference in their entireties including drawings and tables.--

Replace Table 10 beginning at page 171, with the following table:

Table 10

Variance Table

Hugo	GID	OMIM ID	VGX Symbol	Description
	Variance Start	Variance		
U73338	U73338	156570	GEN-69	Methionine
Synthase (SEQ ID NO:1)				
	194	(-201)C>G	5'	
	284	(-111)C>T	5'	
	1136	742G>A	V248M	
	1252	858C>T	Silent	
	1334	940G>A	D314N	
	1699	1305T>C	Silent	
	3150	2756A>G	D919G	
	3207	2813G>T	S938I	
	3209	2815G>C	G939R	
	5444	5050C>A	3'	
	5551	5157G>A	3'	
	5573	5179C>T	3'	
	5659	5265T>C	3'	
	5678	5284T>C	3'	
	5874	5480C>T	3'	
	5934	5540A>G	3'	
D78586	D78586	114010	GEN-BR	CAD PROTEIN (SEQ ID NO:2)
	3434	3408C>T	Silent	
	4313	4287T>C	Silent	
	4799	4773A>G	Silent	
	5255	5229C>T	Silent	
	5455	5429G>A	R1810Q	

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5507	5481T>C	Silent
5810	5784C>T	Silent
6128	6102C>T	Silent
6626	6600C>T	Silent
6686	6660C>T	Silent

U09178 U09178 274270 GEN-HA

Dihydropyrimidine Dehydrogenase (SEQ ID NO:3)

166	85T>C	C29R
577	496A>G	M166V
638	557A>G	Y186C
1708	1627A>G	I543V
3432	3351T>C	3'
3682	3601C>T	3'
3730	3649G>A	3'
3925	3844A>G	3'
3937	3856T>C	3'

U19720 U19720 600424 GEN-II Folate

Transporter (SLC19A1) (SEQ ID NO:4)

175	80G>A	R27H
341	246C>G	Silent
791	696C>T	Silent
1067	972G>A	Silent
1337	1242C>A	Silent
1997	1902T>C	3'
2100	2005^2006insG	3'
2582	2487T>G	3'
2617	2522C>T	3'
2652	2557T>C	3'

U92868 U92868 600424 GEN-LUK Homo sapiens reduced
folate carrier (RFC1) gene, exons 1a, 1c and 1b (SEQ ID NO:5)

431	431A>G	Intron
441	441A>G	Intron
498	498C>T	Intron
579	579G>C	Intron
599	599G>C	Intron

X02308 X02308 188350 GEN-KL Thymidylate

synthetase (SEQ ID NO:6)

1066	961T>C	3'
1136	1031A>G	3'
1497	1392T>A	3'

D00517 D00517 188350 GEN-LUC Thymidylate
synthase, promoter (SEQ ID NO:7)

276	276C>T	Intron
321	321T>C	Intron
452	452G>A	Intron

457	457^insC	Intron
491	491C>A	Intron
533	533T>C	Intron
624	624A>C	Intron
639	639A>G	Intron
655	655T>C	Intron

D00596 D00596 188350 GEN-LUD Homo sapiens
gene for thymidylate synthase, exons 1, 2, 3, 4, 5, 6, 7,
complete cds (SEQ ID NO:8)

701	701A>C	Intron
716	716A>G	Intron
732	732T>C	Intron
1293	1293A>G	Intron
1322	1322C>G	Intron
1379	1379T>C	Intron
1590	1590C>T	Intron
1688	1688C>G	Intron
2401	2401A>G	Intron
2429	2429G>A	Intron
2488	2488C>T	Intron
2594	2594G>T	Intron
2618	2618G>A	Intron
3083	3083G>A	Intron
3125	3125G>A	Intron
3212	3212C>T	Intron
3619	3619T>A	Intron
3635	3635G>A	Intron
4256	4256G>A	Intron
4898	4898A>G	Intron
5006	5006C>T	Intron
5062	5062G>A	Intron
5167	5167G>A	Intron
11069	11069A>G	Intron
11238	11238C>T	Intron
11293	11293T>G	Intron
11422	11422T>C	Intron
11686	11686C>T	Intron
12598	12598T>C	Intron
13171	13171T>C	Intron
13298	13298G>A	Intron
13645	13645T>C	Intron
13751	13751C>A	Intron
13782	13782T>C	Intron
13806	13806T>C	Intron
13813	13813T>C	Intron

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14479	14479A>G	Intron
14546	14546^insT	Intron
14585	14585C>T	Intron
14729	14729G>A	Intron
14787	14787C>T	Intron
14795	14795G>A	Intron
15041	15041T>C	Intron
15343	15343G>A	Intron
15449	15449G>A	Intron
15502	15502G>A	Intron
15545	15545C>T	Intron
15589	15589A>G	Intron
15769	15769C>T	3'
15839	15839A>G	3'
16148	16148G>A	3'
16198	16198T>G	3'
16202	16202G>T	Intron

X59618 X59618 180390 GEN-M3 Ribonucleotide
reductase M2 polypeptide (SEQ ID NO:9)

128	(-67)G>A	5'
189	(-6)T>G	5'
524	330C>G	Silent
1399	1205T>A	3'
1464	1270G>A	3'
1636	1442C>T	3'
1738	1544C>T	3'
2259	2065T>C	3'

S72487 S72487 131222 GEN-3LD Thymidine
phosphorylase, partial (SEQ ID NO:10)

183	19G>A	D7N
483	319C>T	3'
601	437G>C	3'
1299	1135G>A	3'

M58602 M58602 131222 GEN-LUB Thymidine
phosphorylase, promoter and genomic (SEQ ID NO:11)

124	124C>T	3'
439	439G>A	3'
1044	1044^insCT	3'
1331	1331G>A	3'
1977	1977G>A	Intron
2149	2149G>A	Intron
2467	2467A>G	Intron
2634	2634C>G	Intron
2975	2975G>A	Intron
3116	3116G>T	Intron

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3255	3255A>C	Intron
3344	3344T>C	Intron
4051	4051C>A	Intron
4782	4782G>A	Intron
5022	5022T>C	Intron
5266	5266G>A	Intron
5285	5285C>G	Intron
5438	5438T>A	Intron
5482	5482C>T	Intron
5629	5629G>A	Intron
5648	5648C>T	Intron
5731	5731G>A	Intron

M98045 M98045 136510 GEN-4C3 Homo sapiens
folylpolyglutamate synthetase mRNA, complete cds (SEQ ID NO:12)
802 732C>T Silent
1747 1677G>T 3'
1900 1830T>C 3'

U24253 U24253 136510 GEN-LUE Human
folylpolyglutamate synthetase (FPGS) gene, exons 5-11, and
partial cds (SEQ ID NO:13)
1424 1424C>A Intron
1649 1649G>A Intron
2554 2554A>G Intron

U24252 U24252 136510 GEN-LUF
Folylpolyglutamate synthetase, promoter and exons 1-4 (SEQ ID
NO:14)

263	263A>G	Intron
266	266G>T	Intron
527	527C>G	Intron
1037	1037A>G	5'
1139	1139G>A	Intron
1217	1217C>T	Intron
1647	1647C>T	Intron
1955	1955G>A	Intron
2017	2017G>A	Intron
2037	2037G>A	Intron
2189	2189A>G	Intron
2282	2282C>T	Intron
2309	2309A>G	Intron

U09806 U09806 236250 GEN-4FZ Human
methylenetetrahydrofolate reductase mRNA, partial cds (SEQ ID
NO:15)

120	120T>C	Silent
464	464T>G	M155R
519	519C>T	Silent

668	668C>T	A223V		
1059	1059T>C	Silent		
1289	1289C>A	3'		
1308	1308T>C	3'		
1784	1784G>A	3'		
AF061655	AF061655	123920	GEN-LUJ	Cytidine
deaminase, promoter (SEQ ID NO:16)				
575	575T>C	Intron		
648	648T>C	Intron		
771	771G>C	Intron		
883	883G>A	Intron		
941	941^insC	5'		
1051	1051A>C	K27Q		

In the claims

Cancel claim 1-16.

Add new claims 17 - 49

--17. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:6, the probe comprising at least one of:

- (a) nucleotide 1066 wherein N is C;
- (b) nucleotide 1136 wherein N is G;
- (c) nucleotide 1497 wherein N is A;

or the complement thereof.

18. The isolated nucleic acid probe of claim 17 comprising at least two of:

- (a) nucleotide 1066 wherein N is C;
- (b) nucleotide 1136 wherein N is G;
- (c) nucleotide 1497 wherein N is A;

or the complement thereof.

19. The probe of claim 17 comprising no more than 500 contiguous nucleotides of SEQ ID NO:6.

20. The probe of claim 17 comprising no more than 200 contiguous nucleotides of SEQ ID NO:6.

21. The probe of claim 17 comprising no more than 100 contiguous nucleotides of SEQ ID NO:6.

22. The probe of claim 17 comprising no more than 50 contiguous nucleotides of SEQ ID NO:6.

23. The probe of claim 17 comprising DNA.
24. The probe of claim 17 comprising a peptide nucleic acid.
25. The probe of claim 17 further comprising a detectable label.
26. The probe of claim 25 wherein the detectable label is a fluorescent label.
27. A method comprising:
 - (a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient;
 - (b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:6, the probe comprising at least one of:
 - (i) nucleotide 1066 wherein N is C;
 - (ii) nucleotide 1136 wherein N is G;
 - (iii) nucleotide 1497 wherein N is A;
- or the complement thereof; and
- (c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe.

28. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:7, the probe comprising at least one of:
 - (a) nucleotide 276 wherein N is T;
 - (b) nucleotide 321 wherein N is C;
 - (c) nucleotide 452 wherein N is A;
 - (d) C is inserted after nucleotide 457;
 - (e) nucleotide 491 wherein N is A;
 - (f) nucleotide 533 wherein N is C;
 - (g) nucleotide 624 wherein N is C;
 - (h) nucleotide 639 wherein N is G;
 - (i) nucleotide 655 wherein N is C;
- or the complement thereof.

29. The isolated nucleic acid probe of claim 28 comprising at least two of:
 - (a) nucleotide 276 wherein N is T;
 - (b) nucleotide 321 wherein N is C;
 - (c) nucleotide 452 wherein N is A;
 - (d) C is inserted after nucleotide 457;
 - (e) nucleotide 491 wherein N is A;
 - (f) nucleotide 533 wherein N is C;
 - (g) nucleotide 624 wherein N is C;
 - (h) nucleotide 639 wherein N is G;
 - (i) nucleotide 655 wherein N is C;

or the complement thereof.

30. The probe of claim 28 comprising no more than 500 contiguous nucleotides of SEQ ID NO:7.

31. The probe of claim 28 comprising no more than 200 contiguous nucleotides of SEQ ID NO:7.

32. The probe of claim 28 comprising no more than 100 contiguous nucleotides of SEQ ID NO:7.

33. The probe of claim 28 comprising no more than 50 contiguous nucleotides of SEQ ID NO:7.

34. The probe of claim 28 comprising DNA.

35. The probe of claim 28 comprising a peptide nucleic acid.

36. The probe of claim 28 further comprising a detectable label.

37. The probe of claim 36 wherein the detectable label is a fluorescent label.

38. A method comprising:

(a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient;
(b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:7, the probe comprising at least one of:

- (i) nucleotide 276 wherein N is T;
- (ii) nucleotide 321 wherein N is C;
- (iii) nucleotide 452 wherein N is A;
- (iv) C is inserted after nucleotide 457;
- (v) nucleotide 491 wherein N is A;
- (vi) nucleotide 533 wherein N is C;
- (vii) nucleotide 624 wherein N is C;
- (viii) nucleotide 639 wherein N is G;
- (ixi) nucleotide 655 wherein N is C;

or the complement thereof; and

(c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe.

39. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:8, the probe comprising at least one of:

- (a) nucleotide 701 wherein N is C;
- (b) nucleotide 716 wherein N is G;

- (c) nucleotide 732 wherein N is C;
- (d) nucleotide 1293 wherein N is G;
- (e) nucleotide 1322 wherein N is G;
- (f) nucleotide 1379 wherein N is C;
- (g) nucleotide 1590 wherein N is T;
- (h) nucleotide 1688 wherein N is G;
- (i) nucleotide 2401 wherein N is G;
- (j) nucleotide 2429 wherein N is A;
- (k) nucleotide 2488 wherein N is T;
- (l) nucleotide 2594 wherein N is T;
- (m) nucleotide 2618 wherein N is A;
- (n) nucleotide 3083 wherein N is A;
- (o) nucleotide 3125 wherein N is A;
- (p) nucleotide 3212 wherein N is T;
- (q) nucleotide 3619 wherein N is A;
- (r) nucleotide 3635 wherein N is A;
- (s) nucleotide 4256 wherein N is A;
- (t) nucleotide 4898 wherein N is G;
- (u) nucleotide 5006 wherein N is T;
- (v) nucleotide 5062 wherein N is A;
- (w) nucleotide 5167 wherein N is A;
- (x) nucleotide 11069 wherein N is G;
- (y) nucleotide 11238 wherein N is T;
- (z) nucleotide 11293 wherein N is G;
- (aa) nucleotide 11422 wherein N is C;
- (bb) nucleotide 11686 wherein N is T;
- (cc) nucleotide 12598 wherein N is C;
- (dd) nucleotide 13171 wherein N is C;
- (ee) nucleotide 13298 wherein N is A;
- (ff) nucleotide 13645 wherein N is C;
- (gg) nucleotide 13751 wherein N is A;
- (hh) nucleotide 13782 wherein N is C;
- (ii) nucleotide 13806 wherein N is C;
- (jj) nucleotide 13813 wherein N is C;
- (kk) nucleotide 14479 wherein N is G;
- (ll) T is inserted after nucleotide 14546;
- (mm) nucleotide 14585 wherein N is T;
- (nn) nucleotide 14729 wherein N is A;
- (oo) nucleotide 14787 wherein N is T;
- (pp) nucleotide 14795 wherein N is A;
- (qq) nucleotide 15041 wherein N is C;
- (rr) nucleotide 15343 wherein N is A;
- (ss) nucleotide 15449 wherein N is A;
- (tt) nucleotide 15502 wherein N is A;

- (uu) nucleotide 15545 wherein N is T;
- (vv) nucleotide 15589 wherein N is G;
- (ww) nucleotide 15769 wherein N is T;
- (xx) nucleotide 15839 wherein N is G;
- (yy) nucleotide 16148 wherein N is A;
- (zz) nucleotide 16198 wherein N is G; and
- (aaa) nucleotide 16202 wherein N is T;

or the complement thereof.

40. The isolated nucleic acid probe of claim 39 comprising at least two of:

- (a) nucleotide 701 wherein N is C;
- (b) nucleotide 716 wherein N is G;
- (c) nucleotide 732 wherein N is C;
- (d) nucleotide 1293 wherein N is G;
- (e) nucleotide 1322 wherein N is G;
- (f) nucleotide 1379 wherein N is C;
- (g) nucleotide 1590 wherein N is T;
- (h) nucleotide 1688 wherein N is G;
- (i) nucleotide 2401 wherein N is G;
- (j) nucleotide 2429 wherein N is A;
- (k) nucleotide 2488 wherein N is T;
- (l) nucleotide 2594 wherein N is T;
- (m) nucleotide 2618 wherein N is A;
- (n) nucleotide 3083 wherein N is A;
- (o) nucleotide 3125 wherein N is A;
- (p) nucleotide 3212 wherein N is T;
- (q) nucleotide 3619 wherein N is A;
- (r) nucleotide 3635 wherein N is A;
- (s) nucleotide 4256 wherein N is A;
- (t) nucleotide 4898 wherein N is G;
- (u) nucleotide 5006 wherein N is T;
- (v) nucleotide 5062 wherein N is A;
- (w) nucleotide 5167 wherein N is A;
- (x) nucleotide 11069 wherein N is G;
- (y) nucleotide 11238 wherein N is T;
- (z) nucleotide 11293 wherein N is G;
- (aa) nucleotide 11422 wherein N is C;
- (bb) nucleotide 11686 wherein N is T;
- (cc) nucleotide 12598 wherein N is C;
- (dd) nucleotide 13171 wherein N is C;
- (ee) nucleotide 13298 wherein N is A;
- (ff) nucleotide 13645 wherein N is C;
- (gg) nucleotide 13751 wherein N is A;
- (hh) nucleotide 13782 wherein N is C;

- (ii) nucleotide 13806 wherein N is C;
- (jj) nucleotide 13813 wherein N is C;
- (kk) nucleotide 14479 wherein N is G;
- (ll) T is inserted after nucleotide 14546;
- (mm) nucleotide 14585 wherein N is T;
- (nn) nucleotide 14729 wherein N is A;
- (oo) nucleotide 14787 wherein N is T;
- (pp) nucleotide 14795 wherein N is A;
- (qq) nucleotide 15041 wherein N is C;
- (rr) nucleotide 15343 wherein N is A;
- (ss) nucleotide 15449 wherein N is A;
- (tt) nucleotide 15502 wherein N is A;
- (uu) nucleotide 15545 wherein N is T;
- (vv) nucleotide 15589 wherein N is G;
- (ww) nucleotide 15769 wherein N is T;
- (xx) nucleotide 15839 wherein N is G;
- (yy) nucleotide 16148 wherein N is A;
- (zz) nucleotide 16198 wherein N is G; and
- (aaa) nucleotide 16202 wherein N is T;

or the complement thereof.

41. The probe of claim 39 comprising no more than 500 contiguous nucleotides of SEQ ID NO:8.

42. The probe of claim 39 comprising no more than 200 contiguous nucleotides of SEQ ID NO:8.

43. The probe of claim 39 comprising no more than 100 contiguous nucleotides of SEQ ID NO:8.

44. The probe of claim 39 comprising no more than 50 contiguous nucleotides of SEQ ID NO:8.

45. The probe of claim 39 comprising DNA.

46. The probe of claim 39 comprising a peptide nucleic acid.

47. The probe of claim 39 further comprising a detectable label.

48. The probe of claim 47 wherein the detectable label is a fluorescent label.

49. A method comprising:

(a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient;

(b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:8, the probe comprising at least one of:

- (i) nucleotide 701 wherein N is C;
- (ii) nucleotide 716 wherein N is G;
- (iii) nucleotide 732 wherein N is C;
- (iv) nucleotide 1293 wherein N is G;
- (v) nucleotide 1322 wherein N is G;
- (vi) nucleotide 1379 wherein N is C;
- (vii) nucleotide 1590 wherein N is T;
- (viii) nucleotide 1688 wherein N is G;
- (ix) nucleotide 2401 wherein N is G;
- (x) nucleotide 2429 wherein N is A;
- (xi) nucleotide 2488 wherein N is T;
- (xii) nucleotide 2594 wherein N is T;
- (xiii) nucleotide 2618 wherein N is A;
- (xiv) nucleotide 3083 wherein N is A;
- (xv) nucleotide 3125 wherein N is A;
- (xvi) nucleotide 3212 wherein N is T
- (xvii) nucleotide 3619 wherein N is A;
- (xviii) nucleotide 3635 wherein N is A;
- (xix) nucleotide 4256 wherein N is A;
- (xx) nucleotide 4898 wherein N is G;
- (xxi) nucleotide 5006 wherein N is T;
- (xxii) nucleotide 5062 wherein N is A;
- (xxiii) nucleotide 5167 wherein N is A;
- (xxiv) nucleotide 11069 wherein N is G;
- (xxv) nucleotide 11238 wherein N is T;
- (xxvi) nucleotide 11293 wherein N is G;
- (xxvii) nucleotide 11422 wherein N is C;
- (xxviii) nucleotide 11686 wherein N is T;
- (xxix) nucleotide 12598 wherein N is C;
- (xxx) nucleotide 13171 wherein N is C;
- (xxxi) nucleotide 13298 wherein N is A;
- (xxxii) nucleotide 13645 wherein N is C;
- (xxxiii) nucleotide 13751 wherein N is A;
- (xxxiv) nucleotide 13782 wherein N is C;
- (xxxv) nucleotide 13806 wherein N is C;
- (xxxvi) nucleotide 13813 wherein N is C;
- (xxxvii) nucleotide 14479 wherein N is G;
- (xxxviii) T is inserted after nucleotide 14546;
- (xxxix) nucleotide 14585 wherein N is T;
- (xl) nucleotide 14729 wherein N is A;
- (xli) nucleotide 14787 wherein N is T;
- (xlii) nucleotide 14795 wherein N is A;

- (xlivi) nucleotide 15041 wherein N is C;
- (xliv) nucleotide 15343 wherein N is A;
- (xlvi) nucleotide 15449 wherein N is A;
- (xlvi) nucleotide 15502 wherein N is A;
- (xlvii) nucleotide 15545 wherein N is T;
- (xlvii) nucleotide 15589 wherein N is G;
- (xlxi) nucleotide 15769 wherein N is T;
- (I) nucleotide 15839 wherein N is G;
- (li) nucleotide 16148 wherein N is A;
- (lii) nucleotide 16198 wherein N is G; and
- (liii) nucleotide 16202 wherein N is T

or the complement thereof; and

(c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe.--

REMARKS

The amendment to the specification is made solely to insert the Sequence Listing and SEQ ID NOS. into the specification. No new matter is introduced. The accompanying declaration by the inventor confirms that the sequences in the Sequence Listing are the same as those incorporated by reference into the original specification by providing the GenBank® Accession Number for each sequence. A signed declaration will be filed under separate cover.

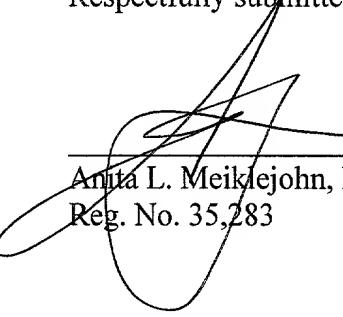
Applicant requests that claims 17-49 be examined together without restriction. Each of SEQ ID NOS:6, 7, and 8 relate to the human thymidylate synthetase gene. SEQ ID NO:6 corresponds to the coding region. SEQ ID NO:7 corresponds to the promoter region. SEQ ID NO:9 corresponds to the exons. Three SEQ ID NOS are required even though only one gene is referenced because the original specification identified the sequences by providing three GenBank® Accession Numbers.

Each of the nucleotides specified in the claims represents a single nucleotide polymorphism in the human thymidylate synthetase gene.

Attached is a marked-up version of the changes being made by the current amendment.

Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,


Anita L. Meiklejohn, Ph.D.
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Version with markings to show changes made

In the specification:

The paragraph beginning at page 1, line 8, has been amended as follows:

This application is a divisional of U.S. Application Serial No. 09/658,659, filed

September 8, 2000, which is a CIP of Stanton, U.S. Application serial No. 09/596,033, filed June 15, 2000 entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton, U.S. Application 09/357,743, filed July 20, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton, U.S. Application Serial No. 09/357,024, filed July 19, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which claims the benefit of Stanton, U.S. Provisional Application 60/093,484, filed July 20, 1998, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which are all hereby incorporated by reference in their entireties including drawings and tables.

Table 10 beginning at page 171 has been amended as follows:

Table 10

Variance Table

Hugo Variance	GID Start	OMIM ID	VGX Symbol	Description
Synthase (SEQ ID NO:1)	194	156570	GEN-69	Methionine
	284	(-201) C>G		5'
	1136	(-111) C>T		5'
	1252	742G>A	V248M	
		858C>T	Silent	

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1334	940G>A	D314N
1699	1305T>C	Silent
3150	2756A>G	D919G
3207	2813G>T	S938I
3209	2815G>C	G939R
5444	5050C>A	3'
5551	5157G>A	3'
5573	5179C>T	3'
5659	5265T>C	3'
5678	5284T>C	3'
5874	5480C>T	3'
5934	5540A>G	3'

D78586 D78586 114010 GEN-BR CAD PROTEIN (SEQ
ID NO:2)

3434	3408C>T	Silent
4313	4287T>C	Silent
4799	4773A>G	Silent
5255	5229C>T	Silent
5455	5429G>A	R1810Q
5507	5481T>C	Silent
5810	5784C>T	Silent
6128	6102C>T	Silent
6626	6600C>T	Silent
6686	6660C>T	Silent

U09178 U09178 274270 GEN-HA
Dihydropyrimidine Dehydrogenase (SEQ ID NO:3)

166	85T>C	C29R
577	496A>G	M166V
638	557A>G	Y186C
1708	1627A>G	I543V
3432	3351T>C	3'
3682	3601C>T	3'
3730	3649G>A	3'
3925	3844A>G	3'
3937	3856T>C	3'

U19720 U19720 600424 GEN-II Folate
Transporter (SLC19A1) (SEQ ID NO:4)

175	80G>A	R27H
341	246C>G	Silent
791	696C>T	Silent
1067	972G>A	Silent
1337	1242C>A	Silent
1997	1902T>C	3'
2100	2005^2006insG	3'
2582	2487T>G	3'

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2617	2522C>T	3'		
2652	2557T>C	3'		
U92868	U92868	600424	GEN-LUK	Homo sapiens reduced folate carrier (RFC1) gene, exons 1a, 1c and 1b <u>(SEQ ID NO:5)</u>
431	431A>G	Intron		
441	441A>G	Intron		
498	498C>T	Intron		
579	579G>C	Intron		
599	599G>C	Intron		
X02308	X02308	188350	GEN-KL	Thymidylate synthetase <u>(SEQ ID NO:6)</u>
1066	961T>C	3'		
1136	1031A>G	3'		
1497	1392T>A	3'		
D00517	D00517	188350	GEN-LUC	Thymidylate synthase, promoter <u>(SEQ ID NO:7)</u>
276	276C>T	Intron		
321	321T>C	Intron		
452	452G>A	Intron		
457	457^insC	Intron		
491	491C>A	Intron		
533	533T>C	Intron		
624	624A>C	Intron		
639	639A>G	Intron		
655	655T>C	Intron		
D00596	D00596	188350	GEN-LUD	Homo sapiens gene for thymidylate synthase, exons 1, 2, 3, 4, 5, 6, 7, complete cds <u>(SEQ ID NO:8)</u>
701	701A>C	Intron		
716	716A>G	Intron		
732	732T>C	Intron		
1293	1293A>G	Intron		
1322	1322C>G	Intron		
1379	1379T>C	Intron		
1590	1590C>T	Intron		
1688	1688C>G	Intron		
2401	2401A>G	Intron		
2429	2429G>A	Intron		
2488	2488C>T	Intron		
2594	2594G>T	Intron		
2618	2618G>A	Intron		
3083	3083G>A	Intron		
3125	3125G>A	Intron		
3212	3212C>T	Intron		
3619	3619T>A	Intron		

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3635	3635G>A	Intron
4256	4256G>A	Intron
4898	4898A>G	Intron
5006	5006C>T	Intron
5062	5062G>A	Intron
5167	5167G>A	Intron
11069	11069A>G	Intron
11238	11238C>T	Intron
11293	11293T>G	Intron
11422	11422T>C	Intron
11686	11686C>T	Intron
12598	12598T>C	Intron
13171	13171T>C	Intron
13298	13298G>A	Intron
13645	13645T>C	Intron
13751	13751C>A	Intron
13782	13782T>C	Intron
13806	13806T>C	Intron
13813	13813T>C	Intron
14479	14479A>G	Intron
14546	14546^insT	Intron
14585	14585C>T	Intron
14729	14729G>A	Intron
14787	14787C>T	Intron
14795	14795G>A	Intron
15041	15041T>C	Intron
15343	15343G>A	Intron
15449	15449G>A	Intron
15502	15502G>A	Intron
15545	15545C>T	Intron
15589	15589A>G	Intron
15769	15769C>T	3'
15839	15839A>G	3'
16148	16148G>A	3'
16198	16198T>G	3'
16202	16202G>T	Intron

X59618	X59618	180390	GEN-M3	Ribonucleotide
reductase M2	polypeptide	<u>(SEQ ID NO:9)</u>		
128		(-67)G>A		5'
189		(-6)T>G		5'
524		330C>G	Silent	
1399		1205T>A		3'
1464		1270G>A		3'
1636		1442C>T		3'
1738		1544C>T		3'

2259 2065T>C 3'
S72487 S72487 131222 GEN-3LD Thymidine
phosphorylase, partial (SEQ ID NO:10)

183 19G>A D7N
483 319C>T 3'
601 437G>C 3'
1299 1135G>A 3'

M58602 M58602 131222 GEN-LUB Thymidine
phosphorylase, promoter and genomic (SEQ ID NO:11)

124 124C>T 3'
439 439G>A 3'
1044 1044^insCT 3'
1331 1331G>A 3'
1977 1977G>A Intron
2149 2149G>A Intron
2467 2467A>G Intron
2634 2634C>G Intron
2975 2975G>A Intron
3116 3116G>T Intron
3255 3255A>C Intron
3344 3344T>C Intron
4051 4051C>A Intron
4782 4782G>A Intron
5022 5022T>C Intron
5266 5266G>A Intron
5285 5285C>G Intron
5438 5438T>A Intron
5482 5482C>T Intron
5629 5629G>A Intron
5648 5648C>T Intron
5731 5731G>A Intron

M98045 M98045 136510 GEN-4C3 Homo sapiens
folylpolyglutamate synthetase mRNA, complete cds (SEQ ID NO:12)
802 732C>T Silent
1747 1677G>T 3'
1900 1830T>C 3'

U24253 U24253 136510 GEN-LUE Human
folylpolyglutamate synthetase (FPGS) gene, exons 5-11, and
partial cds (SEQ ID NO:13)

1424 1424C>A Intron
1649 1649G>A Intron
2554 2554A>G Intron

U24252 U24252 136510 GEN-LUF
Folylpolyglutamate synthetase, promoter and exons 1-4 (SEQ ID NO:14)

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263	263A>G	Intron
266	266G>T	Intron
527	527C>G	Intron
1037	1037A>G	5'
1139	1139G>A	Intron
1217	1217C>T	Intron
1647	1647C>T	Intron
1955	1955G>A	Intron
2017	2017G>A	Intron
2037	2037G>A	Intron
2189	2189A>G	Intron
2282	2282C>T	Intron
2309	2309A>G	Intron

U09806 U09806 236250 GEN-4FZ Human
methylenetetrahydrofolate reductase mRNA, partial cds (SEQ ID
NO:15)

120	120T>C	Silent
464	464T>G	M155R
519	519C>T	Silent
668	668C>T	A223V
1059	1059T>C	Silent
1289	1289C>A	3'
1308	1308T>C	3'
1784	1784G>A	3'

AF061655 AF061655 123920 GEN-LUJ Cytidine
deaminase, promoter (SEQ ID NO:16)

575	575T>C	Intron
648	648T>C	Intron
771	771G>C	Intron
883	883G>A	Intron
941	941^insC	5'
1051	1051A>C	K27Q